II. REMARKS

Formal Matters

Claims 3, 4, 7, 10, 14, 20, 21, 27, 28, 30-35, 37-45, and 47-50 are pending after entry of the amendments set forth herein.

Claims 3, 4, 7, 10, 14, 20, 21, and 27-47 were examined. Claims 4, 7, 10, 14, 20, 21, 27, 29-33, 36, and 40-47 were rejected. Claims 4 and 28 were objected to. Claims 34, 35, and 37-39 were allowed.

Claims 3, 4, 7, 10, 27, 31, and 32 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendments to claims 3, 4, 7, 10, 27, 31, and 32 is found in the claims as originally filed, and throughout the specification, and in particular at the following exemplary locations: paragraphs 0034 and 0073. Accordingly, no new matter is added by these amendments.

Claims 29, 36, and 46 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Claims 48-50 are added. Support for new claims 48-50 is found in the claims as originally filed, and throughout the specification, including the following exemplary locations: claims 48 and 49: paragraph 0070; and claim 50: paragraph 0009. Accordingly, no new matter is added by these new claims.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Office Communication

The Office Communication stated that the amendment filed on November 5, 2004 does not comply with the requirements of 37 C.F.R §1.121(c) because the claim listing contains two marked up claims 13. Applicants presume the Office Communication meant that the amendment filed on November 5, 2004 contained two marked-up claims **3**. Applicants provide herewith a marked-up copy of claim 3, which is in compliance with the requirements of 37 C.F.R.§1.121(c).

This amendment is responsive to the Office Action dated June 2, 2004. Entry of the above-noted

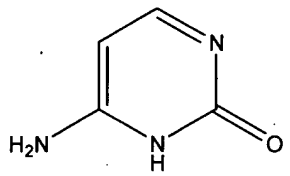
amendments is respectfully requested. In view of the remarks set forth below, reconsideration and allowance of the claims is respectfully requested.

Rejection under 35 U.S.C.§112, first paragraph

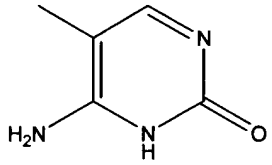
Claims 41-45 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement.

The Office Action stated that the specification does not reasonably provide enablement for a method for reducing a Th2 immune response to a plant allergen in a mammalian subject, the method comprising administering an effective amount of the composition of claim 26, wherein the immunomodulatory nucleic acid comprises the sequence 5'-cytosine-guanine-3'. The Office Action stated that the specification is enabling for the method wherein the immunomodulatory nucleic acid comprises an unmethylated 5'-cytosine-guanine-3' sequence. Applicants respectfully traverse the rejection.

Cytosine has the following structure.



5-methylcytosine has the following structure:



Thus, the term "cytosine" is the structure represented above, and does not include a methyl group found in 5-methylcytosine.

Accordingly, the composition recited in claim 27 is implicitly unmethylated.

Nevertheless, and solely in the interest of expediting prosecution, claim 27 is amended to recite

"wherein the cytosine is unmethylated."

Applicants submit that the rejection of claims 41-45 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§112, second paragraph

Claims 4, 10, 14, 20, 21, 29, 33, 46, and 47 were rejected under 35 U.S.C.§112, second paragraph, as allegedly indefinite.

The Office Action stated that the phrase "derived from" renders claims 10 and claims depending therefrom indefinite. The Office Action stated that claims 4, 29, and 46 recite "a wild type sequence of the non-host species"; and stated that there is no recitation of any non-hose species in the claims from which claims 4, 29, and 36 depend.

Without conceding as to the correctness of this rejection, claim 10 is amended to delete the word "derived." Claims 29 and 46 are canceled without prejudice to renewal, thereby rendering the rejection of these claims moot. Claim 10 and 27 are amended to recite "wherein at least one codon of the nucleic acid sequence encoding the plant allergen is modified from a wild type sequence of the plant allergen to an analogous human codon."

Applicants submit that the rejection of claims 4, 10, 14, 20, 21, 29, 33, 46, and 47 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§102(e)

Claims 7, 10, 14, 27, 30, 33, 36, 40-43, and 47 were rejected under 35 U.S.C.§102(e) as allegedly anticipated by U.S. Patent Publication No. 2003/0035810; "Caplan").

The Office Action stated that 1) Caplan teaches methods and compositions for treating allergic responses in subjects who are allergic to allergens; and 2) Caplan teaches the use of genetically modified microorganisms to express and delivery allergens to a subject. The Office Action stated that due to the open language "comprising" as recited in the instant claims, the polynucleotide compositions can also be present in the form of genetically modified microorganisms. Applicants respectfully traverse the

rejection.

Caplan teaches the use of genetically modified microorganisms to delivery allergens to a mammalian subject. Caplan states that the microorganisms express or produce allergens, and that the microorganisms are taken up by antigen-presenting cells, where the allergens expressed or produced by the microorganisms are released. Caplan, paragraph 0008; and paragraph 0037; paragraph 0040. Caplan states that the microorganisms may act as a natural adjuvant to enhance desirable Th1-type immune responses. Caplan, paragraph 0008; and paragraph 0041.

In contrast, instant claims 10 and 41 recite a method that involves administering a polynucleotide comprising a nucleic acid encoding a plant allergen; and an ISS; and instant claim27 recites a composition comprising a polynucleotide comprising a nucleic acid encoding a plant allergen; and an ISS. The only teaching in Caplan is to administer a microorganism. Accordingly, Caplan cannot anticipate instant claims

Nevertheless, and solely in the interest of expediting prosecution, claims 10 and 27 are amended to recite "an isolated polynucleotide comprising a nucleic acid encoding a plant allergen" and "an isolated polynucleotide comprising an immunomodulatory nucleic acid (ISS)." Caplan neither teaches nor discloses a composition or a use of a composition, wherein the composition comprises an isolated polynucleotide comprising a nucleic acid encoding a plant allergen, and an isolated polynucleotide comprising an ISS. Accordingly, Caplan cannot anticipate claims 10, 27, or 41, or any claim depending, directly or indirectly, from any one of claims 10, 27, and 41.

Applicants submit that the rejection of claims 7, 10, 14, 27, 30, 33, 36, 40-43, and 47 under 35 U.S.C. §102(e) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§102(b)

Claims 27 and 31 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by U.S. Patent No. 5,965,455; "Singh") as evidenced by Schultz et al. ((1987) *Gene* 54:113-123; "Schultz").

The Office Action stated that Singh discloses nucleic acid sequences coding for two ryegrass pollen allergen Lol p Ib family members, and fragments that do not contain native signal sequences. The Office Action stated that Singh teaches suitable vectors for expression in yeast cells include the vector taught by Schultz. The Office Action stated that the yeast expression vector pYEBVC-1 utilized by Schultz for expressing a 400-kD envelope glycoprotein into the culture fluids of JRY188

transformants contains a yeast MFα1 promoter and pre-proleader peptide. The Office Action concluded that the teachings of Singh meet all the claim limitations of the instant claims. Applicants respectfully traverse the rejection.

It is basic patent law that in order to anticipate a claim, a reference must teach each and every element of the claim. *Verdegaal Bros. v. Union Oil of California*, 2USPQ2d 1051, 1053 (Fed. Cir. 1987). A claim is anticipated only if each and every element as set forth in the claim is found in a single prior art reference. Singh alone does not disclose each and every element of claims 27 and 31. Accordingly, Singh cannot anticipate claims 27 and 31.

As discussed in the MPEP§2131.01, there are only three situations in which it is proper to cite multiple references in an anticipation rejection. The three situations are: 1) to prove that the primary reference contains an "enabled disclosure"; 2) to explain the meaning of a term used in the primary reference; or 3) to show that a characteristic not disclosed in the reference is inherent.

The citation of Schultz is not proper in this case, as Schultz is being cited to discuss ayeast expression vector (pYEBVC-1), which is not even mentioned in Singh. Applicants submit that it is not proper in the instant case to cite Schultz along with Singh, and that Singh has to be analyzed as a reference on its own.

Nowhere in Singh is there any disclosure or suggestion of a polynucleotide comprising a nucleic acid encoding a plant allergen modified to include a signal sequence derived from a phylum or kingdom other than a plant phylum. Accordingly, Singh cannot anticipate the instant invention as claimed.

At the passage cited in the Office Action, Singh states:

> Suitable vectors for expression in yeast include YepSec1 (Baldari et al. (1987) *Embo J.* 6:229-234); mPM_ (Kurjan and Herskowitz (1982) *Cell* 30:933-943); and JRY88 (Schultz et al. (1987) *Gene* 54:113-123).

(Singh, column 11, lines18-21).

Singh cites Schultz for JRY88. JRY88 is not a vector. JRY88 is a yeast strain. Schultz, page 114, column 2 under "Yeast manipulations." Singh thus cites Schultz, not for a vector, but for a yeast strain. It is noted that Singh does not incorporate Schultz by reference. Thus, any disclosure in Schultz cannot properly be relied upon in making this rejection.

The Office Action stated that Schultz discusses a yeast expression vector (pYEBVC-1) for expressing a protein that contains a pre-pro-leader polypeptide. However, ***Singh does not disclose the pYEBVC-1 vector***. Singh does not disclose any polynucleotide comprising a nucleic acid encoding a plant allergen, wherein the nucleic acid encoding the plant allergen is operably linked to a signal sequence derived from a non-plant phylum. Accordingly, Singh cannot anticipate claims 27 and 31.

Nevertheless, and solely in the interest of expediting prosecution, claim 27 is amended to recite "wherein at least one codon of the nucleic acid sequence encoding the plant allergen is modified from a wild type sequence of the plant allergen to an analogous human codon." Singh neither discloses nor suggests a polynucleotide composition as recited in claim 27, in which at least one codon of the nucleic acid encoding the plant allergen is modified from a wild type sequence of the plant allergen to an analogous human codon. Accordingly, Singh cannot anticipate claim 27 or claim 31.

Applicants submit that the rejection of claims 27 and 31 under 35 U.S.C. §102(b) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejections under 35 U.S.C.§103(a)

Claims 10, 20, 21, 27, 31, 32, 41, 44, and 45 were rejected under 35 U.S.C.§103(a) as allegedly unpatentable over Caplan in view of WO 98/16247 ("Carson"). Claims 4, 10, 27, 28, 36, and 46 were rejected under 35 U.S.C.§103(a) as allegedly unpatentable over Caplan in view of Kim et al. ((1997) *Gene* 199:293-301; "Kim"). Claims 27 and 30-32 were rejected under 35 U.S.C.§103(a) as allegedly unpatentable over U.S. Patent No. 5,776,761 ("Rogers") in view of Singh and Schultz. Claims 27 and 29 were rejected under 35 U.S.C.§103(a) as allegedly unpatentable over Singh as evidenced by Schultz in view of Kim.

Claims 10, 20, 21, 27, 31, 32, 41, 44, and 45 over Caplan in view of Carson

The Office Action stated that 1) Caplan teaches methods and compositions for treating allergic responses in subjects who are allergic to allergens; 2) Caplan does not specifically teach methods and compositions containing oligonucleotides comprising CpG motifs having the selected nucleotide sequences, and specifically having the sequence AACGTT; and 3) Carson disclosed various CpG motifs that are useful for the induction of Th1-type immune responses. The Office Action stated that it would have been obvious to use the CpG motif containing oligonucleotides taught by Carson in the methods and compositions disclosed by Caplan. Applicants respectfully traverse the rejection.

As discussed above, Caplan does not anticipate claims 10, 27, and 41, or any claim depending therefrom. Caplan teaches the use of genetically modified microorganisms to delivery allergens to a mammalian subject. Caplan states that the microorganisms express or produce allergens, and that the microorganisms are taken up by antigen-presenting cells, where the allergens expressed or produced by the microorganisms are released. Caplan, paragraph 0008; and paragraph 0037; paragraph 0040. Caplan states that the microorganisms may act as a natural adjuvant to enhance desirable Th1-type immune responses. Caplan, paragraph 0008; and paragraph 0041.

As discussed above, claims 10 and 27 are amended to recite to recite "an isolated polynucleotide comprising a nucleic acid encoding a plant allergen" and "an isolated polynucleotide comprising an immunomodulatory nucleic acid (ISS)." Caplan neither teaches nor discloses a composition or a use of a composition, wherein the composition comprises an isolated polynucleotide comprising a nucleic acid encoding a plant allergen, and an isolated polynucleotide comprising an ISS. Accordingly, Caplan cannot anticipate claims 10, 27, or 41, or any claim depending, directly or indirectly, from any one of claims 10, 27, and 41.

As discussed above, claims 10 and 27 are also amended to recite that "at least one codon of the nucleic acid sequence encoding the plant allergen is modified from a wild type sequence of the plant allergen to an analogous human codon." Singh neither discloses nor suggests use of an allergen-encoding polynucleotide that includes at least one codon of the nucleic acid sequence encoding the plant allergen is modified from a wild type sequence of the plant allergen to an analogous human codon.

Carson, in discussing various sequences that induce a Th1-type immune response, does not cure

the deficiency of Caplan. Accordingly, Caplan, alone or in combination with Carson, does not render claims 10, 20, 21, 27, 31, 32, 41, 44, and 45 obvious.

Claims 4, 10, 27, 29, 36, and 46 over Caplan in view of Kim

The Office Action stated that Caplan does not specifically teach methods and compositions containing a polynucleotide wherein at least one codon of the nucleic acid encoding the plant allergen is modified from a wild-type sequence to an analogous codon of a host species. The Office Action stated that Kim teaches that the choice of synonymous codons in many species is strongly biased and that a correlation exists between high expression and the use of selective codons in a given organism. The Office Action stated that it would have been obvious to modify the nucleic acid sequence encoding plan allergens taught by Caplan by substituting codon bases of these nucleic acid sequences with analogous codon bases commonly used in microorganisms to be genetically modified in order to increase expression efficiency of the plant allergens.

Claims 29, 36, and 46 are canceled without prejudice to renewal, thereby rendering the rejection of these claims moot.

As discussed above, claims 10 and 27 are amended to recite that "at least one codon of the nucleic acid sequence encoding the plant allergen is modified from a wild type sequence of the plant allergen to an analogous human codon." Claim 4 is similarly re-worded.

Caplan teaches the use of genetically modified microorganisms to delivery allergens to a mammalian subject. Caplan states that the microorganisms express or produce allergens, and that the microorganisms are taken up by antigen-presenting cells, where the allergens expressed or produced by the microorganisms are released. Caplan, paragraph 0008; and paragraph 0037; paragraph 0040.

There would be no reason for Caplan to have modified at least one codon of the nucleic acid sequence encoding the plant allergen from a wild type sequence of the plant allergen to an analogous human codon, because, as Caplan states, the plant allergen sequences were being expressed in microorganisms, and modifying a codon to an analogous human codon would be expected to result in decreased expression efficiency. If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon* 221 USPQ 1125 (Fed. Cir. 1984).

As such, Caplan, alone or in combination with Kim, cannot render the subject matter of claims 4, 10, 27, 29, 36, and 46 obvious.

Claims 27 and 30-32 over Rogers in view of Singh and Schultz

The Office Action stated that 1) Rogers discloses cDNAs encoding Amb a1 allergic proteins or peptides from ragweed; and teaches techniques to clone as well as produce the allergic protein or peptide in cells; 2) Rogers discloses polynucleotides encoding plant allergens, that also contain CpG sequences; 3) Rogers does not teach the preparation of nucleic acid sequences encoding for Amb a1 allergic proteins or peptides, wherein such nucleic acids contain a heterologous signal sequence; 4) Singh discloses nucleic acid sequences coding for two ryegrass pollen allergen Lol pIb famly members; and 5) Singh teaches suitable vectors such as the vector taught by Schultz. The Office Action concluded that it would have been obvious to clone and express nucleic acids encoding the Amb a1 allergic proteins of Rogers in a yeast expression system taught by Singh and Schultz for the preparation of Amb a1 proteins. Applicants respectfully traverse the rejection.

As noted above, Singh states:

> Suitable vectors for expression in yeast include YepSec1 (Baldari et al. (1987) *Embo J.* 6:229-234); mPM_ (Kurjan and Herskowitz (1982) *Cell* 30:933-943); and JRY88 (Schultz et al. (1987) *Gene* 54:113-123).

(Singh, column 11, lines18-21).

Singh cites Schultz for JRY88. JRY88 is not a vector. JRY88 is a yeast strain. Schultz, page 114, column 2 under "Yeast manipulations." Singh thus cites Schultz, not for a vector, but for a yeast strain. It is noted that Singh does not incorporate Schultz by reference.

The Office Action stated that Schultz discusses a yeast expression vector (pYEBVC-1) for expressing a protein that contains a pre-pro-leader polypeptide. However, ***Singh does not disclose the pYEBVC-1 vecto***r. Singh does not disclose any polynucleotide comprising a nucleic acid encoding a plant allergen, wherein the nucleic acid encoding the plant allergen is operably linked to a signal

sequence derived from a non-plant phylum. Accordingly, Rogers, alone or in combination with Singh, cannot render the subject matter of claims 27 and 30-32 obvious.

Furthermore, as noted above, claim 27 is amended to recite "wherein at least one codon of the nucleic acid sequence encoding the plant allergen is modified from a wild type sequence of the plant allergen to an analogous human codon." Neither Rogers nor Singh discloses or suggest changing the codon usage to human codon bias. As such, Rogers, alone or in combination with Singh, cannot render claims 27 and 30-32 obvious.

Claims 27 and 29 over Singh and Schultz in view of Kim

The Office Action stated that 1) Singh disclose nucleic acid sequences coding for two ryegrass pollen allergen Lol p Ib family members and fragments; 2) Singh provides expression vectors comprising these nucleic acid sequences, including the vector taught by Schultz et al. ((1987) *Gene* 54:113-123); 3) The yeast expression vector utilized by Schultz for expressing a 400-kDa envelope glycoprotein into the culture fluids of JRY188 transformants contain a yeast MFα1 promoter and pre-pro leader polypeptide; 4) Singh does not teach the preparation of nucleic acid sequences coding for two ryegrass pollen allergen Lol p Ib family members, wherein at least one codon of the nucleic acid sequence encoding the allergic antigen is modified to an analogous codon of a host species; and 5) Kim teaches that the choice of synonymous codons in many species is strongly biased and that a correlation exists between high expression and the use of selective codons in a given organism. The Office Action stated that it would have been obvious to modify the nucleic acid sequences encoding ryegrass pollen allergen Lol p Ib family members of Singh by substituting codon bases of these nucleic acids with analogous codon bases commonly used in a given selected expression host cell. Applicants respectfully traverse the rejection.

Claim 29 is canceled without prejudice to renewal, thereby rendering this rejection of claim 29 moot.

As noted above, claim 27 is amended to recite "wherein at least one codon of the nucleic acid sequence encoding the plant allergen is modified from a wild type sequence of the plant allergen to an analogous human codon."

As noted above, Singh states:

> Suitable vectors for expression in yeast include YepSec1 (Baldari et al. (1987) *Embo J.* 6:229-234); mPM_ (Kurjan and Herskowitz (1982) *Cell* 30:933-943); and JRY88 (Schultz et al. (1987) *Gene* 54:113-123).

(Singh, column 11, lines18-21).

Singh cites Schultz for JRY88. JRY88 is not a vector. JRY88 is a yeast strain. Schultz, page 114, column 2 under "Yeast manipulations." Singh thus cites Schultz, not for a vector, but for a yeast strain. It is noted that Singh does not incorporate Schultz by reference.

The Office Action stated that Schultz discusses a yeast expression vector (pYEBVC-1) for expressing a protein that contains a pre-pro-leader polypeptide. However, ***Singh does not disclose the pYEBVC-1 vecto***r. Singh does not disclose any polynucleotide comprising a nucleic acid encoding a plant allergen, wherein the nucleic acid encoding the plant allergen is operably linked to a signal sequence derived from a non-plant phylum.

Schultz is merely concerned with expression in yeast. There is no motivation in Schultz to modify a codon of a plant allergen-encoding nucleic acid to an analogous human codon.

Singh neither discloses nor suggest modifying a codon of a plant allergen-encoding nucleic acid to an analogous human codon. Singh states that that invention described therein provides purified nucleic acid sequences coding for a Lol p Ib ryegrass pollen allergen; and host cells transformed to express a protein or peptide encoded by the nucleic acids. Singh, column 3, lines 10-22. Singh states that antigenic fragments of Lol p Ib proteins are useful for inducing T cell anergy. Singh, column 9, lines 47-51; and column 10, lines 35-41. Singh states that expression vectors comprising the Lol p Ib nucleic acids can be introduced into host cells, for the purpose of preparing recombinant Lol p Ib proteins. Singh, column 11, lines 1-21; and column 11, line 56 to column 12, line 5. Not one of the host cells recited in Singh is a human host cell. Singh, column 11, lines 1-21. Thus, there is no disclosure or suggestion in Singh to modify a codon of a plant allergen-encoding nucleic acid to an analogous human codon.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones,* 21 USPQ2d 1941 (Fed. Cir. 1992). Second, there must be a reasonable expectation of success. *In re Merck & Co., Inc.*, 231 USPQ 375 (Fed. Cir. 1986). Finally, the prior art reference, or references when combined, must teach or suggest all the claim limitations. *In re Royka*, 180 USPQ 580 (CCPA 1974). All three criteria must be met. If any one of these three criteria is not met, a *prima facie* case of obviousness has not been established.

There is no motivation in the cited references to combine the reference teachings. Singh is concerned with a particular allergen, and its use to induce T cell anergy; and mentions the use of various non-human host cells for production of the allergen. There is no motivation in Singh to modify a codon of a plant allergen-encoding nucleic acid to an analogous human codon. Schultz is merely concerned with expression in yeast. There is no motivation in Schultz to modify a codon of a plant allergen-encoding nucleic acid to an analogous human codon. Kim is merely a general reference discussing codon usage. There is no motivation in Kim to modify a codon of a plant allergen-encoding nucleic acid to an analogous human codon.

Accordingly, Singh, alone or in combination with Kim, does not render claims 27 and 29 obvious.

Conclusion as to the rejections under 35 U.S.C.§103(a)

Applicants submit that the rejection of claims discussed above under 35 U.S.C. §103(a) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL203.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Apr. 15, 2005

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